



General

Guideline Title

Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder: a clinical practice guideline from the American College of Physicians.

Bibliographic Source(s)

Qaseem A, Barry MJ, Kansagara D, Clinical Guidelines Committee of the American College of Physicians. Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2016 Mar 1;164(5):350-9. [71 references] [PubMed](#)

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions for the overall quality of evidence (high, moderate, low, or insufficient evidence to determine net benefits or risks) and the strength of the recommendations (strong, weak) are provided at the end of the "Major Recommendations" field.

Recommendation: The American College of Physicians (ACP) recommends that clinicians select between either cognitive behavioral therapy (CBT) or second-generation antidepressants (SGAs) to treat patients with major depressive disorder (MDD) after discussing treatment effects, adverse effect profiles, cost, accessibility, and preferences with the patient. (Grade: strong recommendation, moderate-quality evidence)

Moderate-quality evidence shows that CBT and SGAs are similarly effective treatments for MDD. Moderate-quality evidence suggests that discontinuation rates are similar for CBT and SGAs, although discontinuation due to adverse events is non-statistically significantly increased with SGAs. However, harms associated with SGAs are probably underrepresented in the included trials. Thus, ACP concludes that CBT has no more—and probably fewer—adverse effects than SGAs. In addition, lower relapse rates have been reported with CBT than SGAs. Although SGAs are often initially prescribed for patients with depression, CBT is a reasonable approach for initial treatment and should be strongly considered as an alternative treatment to SGAs where available. Further, there are reported differences among SGAs in mild (constipation, diarrhea, dizziness, headache, insomnia, nausea, and somnolence) to major (sexual dysfunction and suicidality) adverse effects. Bupropion is associated with a lower rate of sexual adverse events than fluoxetine and sertraline, whereas paroxetine has higher rates of sexual dysfunction than fluoxetine, fluvoxamine, nefazodone, and sertraline. Physicians and patients should discuss adverse event profiles before selecting a medication.

Definitions

Grading of Quality of Evidence

High-Quality Evidence: Evidence is considered high quality when it is obtained from 1 or more well-designed and well-executed randomized controlled trials (RCTs) that yield consistent and directly applicable results. This also means that further research is very unlikely to change confidence in the estimate of effect.

Moderate-Quality Evidence: Evidence is considered moderate quality when it is obtained from RCTs with important limitations—for example, biased assessment of the treatment effect, large loss to follow-up, lack of blinding, unexplained heterogeneity (even if it is generated from rigorous RCTs), indirect evidence originating from similar (but not identical) populations of interest, and RCTs with a very small number of participants or observed events. In addition, evidence from well-designed controlled trials without randomization, well-designed cohort or case-control analytic studies, and multiple time series with or without intervention are in this category. Moderate-quality evidence also means that further research will probably have an important effect on confidence in the estimate of effect and may change the estimate.

Low-Quality Evidence: Evidence obtained from observational studies would typically be rated as low quality because of the risk for bias. Low-quality evidence means that further research is very likely to have an important effect on confidence in the estimate of effect and will probably change the estimate. However, the quality of evidence may be rated as moderate or even high, depending on circumstances under which evidence is obtained from observational studies. Factors that may contribute to upgrading the quality of evidence include a large magnitude of the observed effect, a dose-response association, or the presence of an observed effect when all plausible confounders would decrease the observed effect.

Insufficient Evidence to Determine Net Benefits or Risks: When the evidence is insufficient to determine for or against routinely providing a service, the recommendation was graded as "insufficient evidence to determine net benefits or risks." Evidence may be conflicting, of poor quality, or lacking, and hence the balance of benefits and harms cannot be determined. Any estimate of effect that is very uncertain as evidence is either unavailable or does not permit a conclusion.

The American College of Physicians' Guideline Grading System*

Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced With Risks and Burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks		

*Adopted from the classification developed by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) workgroup.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Major depressive disorder (MDD)

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Psychiatry

Psychology

Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To summarize and grade the evidence on the comparative effectiveness and safety of nonpharmacologic treatments and second-generation antidepressants (SGAs) (including serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, bupropion, mirtazapine, nefazodone, and trazodone), alone or in combination, for major depressive disorder (MDD)

Target Population

All adults (aged ≥ 18 years) with major depressive disorder (MDD)

Interventions and Practices Considered

1. Cognitive behavioral therapy (CBT)
2. Second-generation antidepressants (SGAs)

Note: Complementary and alternative medicine (CAM) treatments were considered but not recommended.

Major Outcomes Considered

- Response (often defined as $\geq 50\%$ improvement in Hamilton Depression Rating Scale [HAM-D] scores)
- Remission (often defined as a HAM-D score ≤ 7)
- Speed of response
- Speed of remission
- Relapse
- Quality of life
- Functional capacity (as assessed by various scales)
- Reduction of suicidality
- Reduction of hospitalization

- Overall adverse events

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): A systematic evidence review was prepared by the RTI International–University of North Carolina Evidence-based Practice Center (EPC) (see the "Availability of Companion Documents" field).

Data Sources and Searches

The investigators searched MEDLINE (via PubMed), EMBASE, the Cochrane Library, the Allied and Complementary Medicine Database, PsycINFO, and CINAHL from January 1990 to 23 September 2015. They used a combination of Medical Subject Heading terms and keywords, focusing on terms to describe the relevant population and interventions of interest. They limited electronic searches to "adult 19+ years"; "human"; and "English, German, and Italian languages." Table 1 of the Supplement (see the "Availability of Companion Documents" field) shows the electronic search strategy. To detect unpublished studies, the investigators searched ClinicalTrials.gov, the World Health Organization's International Clinical Trials Registry Platform, Drugs @FDA, the European Medicines Agency, the National Institute of Mental Health Web site, the American Psychological Association Web site, Scopus, the Conference Proceedings Citation Index, and reference lists of pertinent reviews and included trials.

The Agency for Healthcare Research and Quality (AHRQ) Scientific Resource Center requested scientific information packets from relevant manufacturing companies, asking for any unpublished studies or relevant data. The investigators received information packets from Eli Lilly and Company (Indianapolis, Indiana) and Merck & Co. (Kenilworth, New Jersey).

To obtain unreported data from published trials, the investigators contacted authors.

Study Selection

Two trained team members independently reviewed all abstracts and full-text articles by using predefined inclusion and exclusion criteria. The population of interest was adult outpatients of all races and ethnicities with major depressive disorder (MDD) during 1) an initial treatment attempt or 2) a second treatment attempt in patients who did not achieve remission after treatment with a second-generation antidepressant (SGA). For patients with an initial treatment attempt, they were interested in the benefits and harms of SGAs compared with common depression-focused psychological interventions, complementary and alternative medicine (CAM) interventions, and exercise as 1) monotherapies, 2) in combination with one another, or 3) in combination with a SGA. For patients who did not achieve remission after an adequate trial with a SGA, they were interested in second-step therapies that could involve a switch to a new treatment or an augmentation of an existing treatment with a pharmacologic or nonpharmacologic option. The table in the systematic review shows the interventions that the investigators reviewed.

To assess the comparative benefits, the investigators limited studies to randomized controlled trials (RCTs) of at least 6 weeks' duration that compared 2 interventions of interest. In general, they included only double blinded RCTs. For interventions for which double blinding was not possible (such as psychological interventions or yoga), they required that outcomes assessors be blinded. For harms (evidence pertaining to safety, tolerability, and adverse events), the investigators intended to examine data from both randomized and nonrandomized studies (minimum sample size of 500), but found no eligible nonrandomized studies.

The investigators excluded studies that both reviewers agreed did not meet eligibility criteria. Investigators resolved disagreements about inclusion or exclusion by consensus or by involving a third reviewer. Detailed inclusion and exclusion criteria are presented in the AHRQ report (see the "Availability of Companion Documents" field).

Number of Source Documents

The searches identified 8316 citations (see Appendix Figure in the systematic review [see the "Availability of Companion Documents" field]). Forty-five head-to-head trials (56 publications) were included. To obtain unreported data from published trials, the investigators contacted authors. Additional outcomes data were obtained for 10 trials.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Grading of Quality of Evidence

High-Quality Evidence: Evidence is considered high quality when it is obtained from 1 or more well-designed and well-executed randomized controlled trials (RCTs) that yield consistent and directly applicable results. This also means that further research is very unlikely to change confidence in the estimate of effect.

Moderate-Quality Evidence: Evidence is considered moderate quality when it is obtained from RCTs with important limitations—for example, biased assessment of the treatment effect, large loss to follow-up, lack of blinding, unexplained heterogeneity (even if it is generated from rigorous RCTs), indirect evidence originating from similar (but not identical) populations of interest, and RCTs with a very small number of participants or observed events. In addition, evidence from well-designed controlled trials without randomization, well-designed cohort or case-control analytic studies, and multiple time series with or without intervention are in this category. Moderate-quality evidence also means that further research will probably have an important effect on confidence in the estimate of effect and may change the estimate.

Low-Quality Evidence: Evidence obtained from observational studies would typically be rated as low quality because of the risk for bias. Low-quality evidence means that further research is very likely to have an important effect on confidence in the estimate of effect and will probably change the estimate. However, the quality of evidence may be rated as moderate or even high, depending on circumstances under which evidence is obtained from observational studies. Factors that may contribute to upgrading the quality of evidence include a large magnitude of the observed effect, a dose-response association, or the presence of an observed effect when all plausible confounders would decrease the observed effect.

Insufficient Evidence to Determine Net Benefits or Risks: When the evidence is insufficient to determine for or against routinely providing a service, the recommendation was graded as "insufficient evidence to determine net benefits or risks." Evidence may be conflicting, of poor quality, or lacking, and hence the balance of benefits and harms cannot be determined. Any estimate of effect that is very uncertain as evidence is either unavailable or does not permit a conclusion.

Methods Used to Analyze the Evidence

Meta-Analysis

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): A systematic evidence review was prepared by the RTI International–University of North Carolina Evidence-based Practice Center (EPC) (see the "Availability of Companion Documents" field).

Data Extraction and Quality Assessment

The investigators designed, pilot-tested, and used a structured data abstraction form to ensure consistency of data abstraction. Trained reviewers initially abstracted data from each study. A senior reviewer evaluated the completeness and accuracy of the data abstraction.

The investigators classified patients' severity of depression by using the categorization systems of the University of Pittsburgh Epidemiology Data Center and Zimmerman and colleagues.

To assess the risk of bias of studies, the investigators used definitions based on Agency for Healthcare Research and Quality (AHRQ) guidance. They rated the risk of bias for each relevant outcome of a study as low, moderate, or high. To determine risk of bias in a standardized way, they used the Cochrane Risk of Bias tool to appraise randomized controlled trials (RCTs). Two independent reviewers assigned risk-of-bias ratings. They resolved any disagreements by discussion and consensus or by consultation with a third reviewer.

Data Synthesis and Analysis

To determine whether meta-analyses were appropriate, the investigators assessed the clinical and methodological heterogeneity of the studies under consideration by following established guidance. They combined studies that were similar in populations and interventions, and assessed outcomes at similar follow-up times (most commonly 8 to 16 weeks). For all analyses, they used random- and fixed-effects models to estimate comparative effects. The investigators used restricted maximum likelihood models for random-effects analyses.

For efficacy, the investigators conducted meta-analyses on the relative risk for achieving response (as defined by the study authors, most commonly as a $\geq 50\%$ improvement from baseline) on the Hamilton Rating Scale for Depression (HAM-D) or the Montgomery–Åsberg Depression Rating Scale at study end point, and the relative risk for achieving remission (as defined by the study authors, most commonly as a HAM-D score < 7) at study end point. For harms, they conducted meta-analyses on the relative risk for experiencing an adverse event, discontinuing treatment, and discontinuing treatment because of harms.

For each meta-analysis, the investigators tested for heterogeneity by using the Cochran Q test and estimated the extent of heterogeneity with the I^2 statistic (the proportion of variation in study estimates attributable to heterogeneity). If heterogeneity was high ($> 60\%$), they explored differences in clinical and methodological characteristics among studies considered for meta-analyses.

Previous investigations have demonstrated that no substantial differences in benefits and harms exist among second-generation antidepressants (SGAs); therefore, in all meta-analyses, they compared SGAs as a class with other interventions of interest. The investigators categorize types of psychological interventions according to the Cochrane Depression, Anxiety and Neurosis Review Group classification system.

For all meta-analyses, the investigators conducted sensitivity analyses with and without high risk-of-bias studies.

They assessed publication bias by using funnel plots and Kendall τ rank correlation. However, given the small number of component studies in the meta-analyses, these tests have low sensitivity to detect publication bias. They conducted meta-analyses by using OpenMetaAnalyst.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Note from the National Guideline Clearinghouse (NGC): A systematic evidence review was prepared by the RTI International–University of North Carolina Evidence-based Practice Center (EPC) (see the "Availability of Companion Documents" field).

This guideline is based on a systematic evidence review, an update of the literature (see the Supplement), and an evidence report sponsored by the Agency for Healthcare Research and Quality (AHRQ) (see the "Availability of Companion Documents" field) that addressed the following key questions:

- 1a. In adult patients with major depressive disorder (MDD) who are undergoing an initial treatment attempt, what is the effectiveness of second-generation antidepressant (SGA) monotherapy compared with the effectiveness of either nonpharmacological monotherapy or combination therapy (involving nonpharmacological treatments with or without an SGA)?
- 1b. Does comparative treatment effectiveness vary by MDD severity?
- 2a. In adult patients with MDD who did not achieve remission following an initial adequate trial with one SGA, what is the comparative effectiveness of second-step therapies?
- 2b. Does comparative treatment effectiveness vary by MDD severity?
- 3a. In adult patients with MDD, what are the comparative risks of harms of these treatment options for those undergoing an initial treatment attempt or those who did not achieve remission following an initial adequate trial with an SGA?
- 3b. Do the comparative risks of treatment harms vary by MDD severity?
- 4. Do the benefits and risks of harms of these treatment options differ by subgroups of patients with MDD defined by common accompanying psychiatric symptoms (coexisting anxiety, insomnia, low energy, or somatization) or demographic characteristics (age, sex,

race, or ethnicity)?

This guideline rates the evidence and recommendations by using the American College of Physicians' (ACP's) guideline grading system (see the "Rating Scheme for the Strength of the Evidence" and "Rating Scheme for the Strength of the Recommendations" fields). Details of the guideline development process can be found in the ACP methods paper (see the "Availability of Companion Documents" field).

Rating Scheme for the Strength of the Recommendations

The American College of Physicians' Guideline Grading System*

Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced With Risks and Burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks		

*Adopted from the classification developed by the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) workgroup.

Cost Analysis

Published cost analyses were reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

The guideline underwent a peer review process through the journal and was posted online for comments from American College of Physicians (ACP) Governors and Regents.

This guideline was approved by the ACP Board of Regents on November 7, 2015.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of nonpharmacologic and pharmacologic treatment for adults with major depressive disorder (MDD)

See the original guideline document for comparative benefits of different treatments.

Potential Harms

Harms assessed included overall adverse events, withdrawals because of adverse events, serious adverse events, specific adverse events (including hyponatremia, seizures, suicidality, hepatotoxicity, weight gain, gastrointestinal symptoms, and sexual adverse events), withdrawals because of specific adverse events, or drug interactions.

Contraindications

Contraindications

St. John's wort is contraindicated in patients receiving monoamine oxidase or serotonin reuptake inhibitors.

Qualifying Statements

Qualifying Statements

- Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All American College of Physicians (ACP) clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication or once an update has been issued.
- The authors of this article are responsible for its contents, including any clinical or treatment recommendations.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Mobile Device Resources

Patient Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Qaseem A, Barry MJ, Kansagara D, Clinical Guidelines Committee of the American College of Physicians. Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2016 Mar 1;164(5):350-9. [71 references] [PubMed](#)

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 Mar 1

Guideline Developer(s)

American College of Physicians - Medical Specialty Society

Source(s) of Funding

Financial support for the development of this guideline comes exclusively from the American College of Physicians (ACP) operating budget.

Guideline Committee

Clinical Guidelines Committee of the American College of Physicians

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

All financial and intellectual disclosures of interest were declared and potential conflicts were discussed and managed. Dr. Forciea was recused from voting on this guideline and from chairing during the discussion of the guideline for an active indirect financial conflict. Dr. Manaker was recused from voting on the guideline for an active indirect financial conflict. Dr. Vijan was recused from voting on the guideline for an active direct

intellectual conflict. Authors not named here have disclosed no conflicts of interest. Authors followed the policy regarding conflicts of interest described at www.annals.org/article.aspx?articleid=745942 . Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M15-2570 . A record of disclosures of interest and management of conflicts of interest is kept for each Clinical Guidelines Committee meeting and conference call and can be viewed at www.acponline.org/clinical_information/guidelines/guidelines/conflicts_cgc.htm .

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the [Annals of Internal Medicine Web site](#) .

Availability of Companion Documents

The following are available:

- Gartlehner G, Gaynes BN, Amick HR, Asher GN, Morgan LC, Coker-Schwimmer E, Ferneris C, Boland E, Lux LJ, Gaylord S, Bann C, Pierl CB, Lohr KN. Comparative benefits and harms of antidepressant, psychological, complementary, and exercise treatments for major depression: an evidence report for a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2016 Mar 1;164(5):331-41. Available from the [Annals of Internal Medicine Web site](#) .
- Comparative benefits and harms of antidepressant, psychological, complementary, and exercise treatments for major depression: an evidence report for a clinical practice guideline from the American College of Physicians. Supplement. 2016. 29 p. Available from the [Annals of Internal Medicine Web site](#) .
- Gartlehner G, Gaynes BN, Amick HR, Asher G, Morgan LC, Coker-Schwimmer E, Forneris C, Boland E, Lux LJ, Gaylord S, Bann C, Pierl CB, Lohr KN. Nonpharmacological versus pharmacological treatments for adult patients with major depressive disorder. Comparative effectiveness review no. 161. (Prepared by the RTI International–University of North Carolina Evidence-based Practice Center under Contract No. 290-2012-00008-I.) AHRQ Publication No. 15(16)-EHC031-EF. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2015 Dec. 274 p. Available from the [Agency for Healthcare Research and Quality \(AHRQ\) Web site](#) .
- Qaseem A, Snow V, Owens DK, Shekelle P. The development of clinical practice guidelines and guidance statements of the American College of Physicians: summary of methods. *Ann Intern Med*. 2010 Aug 3;153(3):194-9. Available from the [Annals of Internal Medicine Web site](#) .

A collection of Recommendation Summaries for all current American College of Physicians (ACP) Clinical Guidelines is now available for mobile devices from the [ACP Web site](#) .

Patient Resources

The following is available:

- Medicine and nonmedicine options for the treatment of adults with major depressive disorder. Summaries for patients. *Ann Intern Med*. 2016 Mar 1;164(5):I-18. Available from the [Annals of Internal Medicine Web site](#) .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original

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NGC Status

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